PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness and safety of ivermectin in the treatment of COVID-19: protocol for a systematic review and meta-analysis
AUTHORS	Machado, Maria; Souza, Amaxsell; Linhares, Paula Vívian; Martins Ferreira, Caio; Franciole, David; Martins, Rand; Cobucci, Ricardo

VERSION 1 – REVIEW

REVIEWER	Yang, Shu Chengdu University of Traditional Chinese Medicine
REVIEW RETURNED	23-Apr-2021

GENERAL COMMENTS	Since the total number and sample size of the included studies are not yet known, it is not possible to estimate the stability and reproducibility of the study. Although I have not seen anything about the limitations of this study in the discussion section, these can be discussed after the study is basically completed.

REVIEWER	Sun, J
REVIEW RETURNED	22-Jun-2021

GENERAL COMMENTS	Overall, the study protocol is well designed and presented, and the statistical analysis is detailed described. I only have a few minor points with regard to this paper. 1) In the abstract, the author stated that "meta-analysis will then be carried out using a random-effects model", but in the Section of Data analysis it was stated as 'using RevMan software with the inverse variance method and a random-effects model if more than 50% heterogeneity is identified'. The inverse variance method is one of the approaches of the fixed-effects model. Therefore, the author should describe consistently the synthesis method. In my opinion, both fixed-effects and random-effects results can be presented, regardless of heterogeneity analysis. 2) The author did not describe clearly how sensitivity analysis was performed. 3) For dichotomous variables, I would recommend that the author select only one effect estimate (RR, OR) because RR and OR are somewhat different. 4) For participants, it is not clear how "people at risk of exposure to the virus" were defined.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Shu Yang, Chengdu University of Traditional Chinese Medicine

Since the total number and sample size of the included studies are not yet known, it is not possible to estimate the stability and reproducibility of the study. Although I have not seen anything about the limitations of this study in the discussion section, these can be discussed after the study is basically completed.

Response: We appreciate the comments, since as noted by the reviewer, the limitations of the study will be better defined after the collection and analysis of the literature. However, we added a likely limitation of this study in the discussion section: “A possible limitation of this study is that clinical trials with low number of participants, or events, or both, leading to wide confidence intervals and high uncertainty of the estimated effects can compromise the level of evidence generated in this meta-analysis.”

Reviewer: 2
Dr. J Sun

Overall, the study protocol is well designed and presented, and the statistical analysis is detailed described. I only have a few minor points with regard to this paper.
1) In the abstract, the author stated that "meta-analysis will then be carried out using a random-effects model", but in the Section of Data analysis it was stated as 'using RevMan software with the inverse variance method and a random-effects model if more than 50% heterogeneity is identified'. The inverse variance method is one of the approaches of the fixed-effects model. Therefore, the author should describe consistently the synthesis method. In my opinion, both fixed-effects and random-effects results can be presented, regardless of heterogeneity analysis.
Response: We appreciate the comment. We agree with the reviewer and change the abstract following all their recommendations:” Meta-analysis will then be carried out using fixed or random effects model, using the mean difference for continuous outcomes and the relative risk for dichotomous outcomes”.
“Data synthesis
In the event of inclusion of three or more RCTs, we will perform a quantitative synthesis (meta-analysis) using RevMan 5.3.528 software with the fixed-effects or random-effects model if more than 50% heterogeneity is identified among studies.”

2) The author did not describe clearly how sensitivity analysis was performed.
Response: We appreciate the comment. We agree with the reviewer, and we improved in the revised manuscript the explanation of how the sensitivity analysis will be carried out:” The primary analysis will include only those studies that had low risk or some concerns of bias according to the RoB 2 assessment. We will include high risk of bias studies in a secondary analysis to assess the impact on the results.”

3) For dichotomous variables, I would recommend that the author select only one effect estimate (RR, OR) because RR and OR are somewhat different.
Response: We appreciate the comment. We agree with the reviewer and change the measures of treatment effect following all their recommendations: “For dichotomous variables, we will analyze the relative risk (RR) with the respective 95% confidence intervals (CIs).”

4) For participants, it is not clear how "people at risk of exposure to the virus" were defined.

Response: We appreciate the comment. We agree with the reviewer, and we added the explanation: “people at risk of exposure to the virus (people having “high-risk” contact with patients with confirmed COVID-19)”.

VERSION 2 – REVIEW

REVIEWER	Sun, J
REVIEW RETURNED	22-Aug-2021

GENERAL COMMENTS	The authors have addressed the reviewer's comments and the manuscript is improved greatly. I have no further comments.